Sleep Medicine 15 (2014) 459–463

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Vitamin D levels and obstructive sleep apnoea in children

Leila Kheirandish-Gozal *, Eduard Peris, David Gozal *

Section of Sleep Medicine, Department of Pediatrics, Pritzker School of Medicine, Biological Sciences Division, The University of Chicago, Chicago, IL, USA

ARTICLE INFO

Article history:
Received 12 September 2013
Received in revised form 14 December 2013
Accepted 17 December 2013
Available online 7 February 2014

Keywords:
Vitamin D
Sleep apnoea
Children
Metabolism
Insulin resistance
Systemic inflammation

ABSTRACT

Aims/hypothesis: Obstructive sleep apnoea (OSA) is a common health problem in children. African American (AA) and obese children have higher prevalence of OSA, and are also at a higher risk of reduced vitamin D levels. We hypothesised that OSA would be associated with lower levels of plasma 25-hydroxyvitamin D (25(OH)D) and increase in the risk of metabolic dysfunction and systemic inflammation.
Methods: In this observational cross-sectional study, 176 prospectively recruited children (mean age: 6.8 ± 0.8 years) underwent overnight polysomnographic evaluation and a fasting blood draw the morning after the sleep study. In addition to lipid profile, homeostatic model of insulin resistance (HOMA-IR) and high-sensitivity C-reactive protein (hsCRP) assays and plasma 25(OH)D levels were assessed using ELISA kits.
Results: AA children, obese children and children with OSA had significantly lower 25(OH)D levels. Linear associations emerged between 25(OH)D plasma levels and body mass index (BMI) *z*-score, hsCRP and HOMA-IR, as well as with apnoea–hypopnoea index (AHI) and oxygen saturation (SpO_2) nadir, the latter two associations remaining statistically significant even when controlling for all other potential confounders, and independently accounting for 17.7% of the variance in 25(OH)D ($p < 0.01$).
Conclusions: 25(OH)D levels are reduced in paediatric OSA, in AA children and in obese children, particularly when all are present, and may play a role in modulating the degree of insulin resistance and systemic inflammation. The short-term and long-term significance of reduced 25(OH)D in paediatric OSA remains undefined.

1. Introduction

Obstructive sleep apnoea (OSA) is a prevalent health problem in children affecting up to 3–4% of all children, with African American (AA) and obese children being at a particularly higher risk [1]. It has become apparent that OSA is strongly associated with the presence of insulin resistance and altered lipid homeostasis, as well as with systemic inflammation and endothelial dysfunction and an increased prevalence of respiratory illnesses that lead to higher health-care utilization costs [2–5].

Similar to OSA, low vitamin D levels, as indicated by concentrations of serum 25-hydroxyvitamin D (25(OH)D), have been linked to increases in the frequency and severity of metabolic dysfunction, cardiovascular disease risk factors as well as with an increased incidence of upper respiratory tract infections [6–15]. Interventions aimed at increased 25(OH)D concentrations have resulted in improvements in these outcomes [15]. Furthermore, a recent preliminary study suggested that children at risk of adenotonsillectomy may exhibit lower serum 25(OH)D concentrations [16], even if such findings were not replicated in another small cohort [17].

We hypothesised that OSA in children would be associated with reduced plasma levels of 25(OH)D, particularly in obese children and in AA children. Furthermore, we postulated that significant associations between sleep measures and 25(OH)D would emerge and be independent of confounding factors, such as body mass index (BMI) *z*-score, serum lipids, high-sensitivity C-reactive protein (hsCRP) and a measure of insulin resistance (i.e., the homeostatic model of insulin resistance – HOMA-IR).

2. Materials and methods

The research protocol was approved by the University of Chicago (protocol 09-115-B) Human Research Ethics Committee. Informed consent was obtained from the parents, and age-appropriate assent was also obtained from the children. Children were recruited from the Sleep and ENT clinics at Comer Children's Hospital, as well as by advertisement in the community. Those children who had genetic or craniofacial syndromes and chronic diseases, such as cardiac disease, diabetes, cerebral palsy and chronic lung disease of prematurity, were excluded.

* Corresponding authors. Address: Section of Pediatric Sleep Medicine, Department of Pediatrics, Pritzker School of Medicine, The University of Chicago, 5841 S. Maryland Avenue/MC2117, Chicago, IL 60637-1470, USA. Tel.: +1 (773) 834 3815; fax: +1 (773) 834 1444.

E-mail addresses: lgozal@peds.bsd.uchicago.edu (L. Kheirandish-Gozal), dgozal@uchicago.edu (D. Gozal).

http://dx.doi.org/10.1016/j.sleep.2013.12.009
1389-9457/

2.1. Overnight polysomnographic studies

All children underwent standard overnight nocturnal polysomnogram (NPSG) evaluation as previously described [18], with assessment of eight standard electroencephalography (EEG) channels, bilateral electro-oculogram (EOG), electromyogram (EMG), 2-lead electrocardiography (ECG), oronasal airflow measurement using thermistor, nasal pressure transducer and end tidal CO_2, chest and abdominal movement by respiratory inductance plethysmography and pulse oximetry including pulse waveform using a commercially available data acquisition system (Polysmith; Nihon Kohden America Inc., CA, USA). The NPSG studies were scored according to the 2007 American Association of Sleep Medicine guidelines for the scoring of sleep and associated events [19]. The proportion of time spent in each stage of sleep was calculated as a percentage of total sleep time (TST). A respiratory event was scored as an obstructive apnoea if it was associated with a >90% fall in signal amplitude for >90% of the entire event compared to the baseline amplitude, the event lasted for at least two breaths and there was continued or increased respiratory effort throughout the period of the event. A mixed apnoea was scored if inspiratory effort was absent in the initial part of the event, followed by resumption of inspiratory effort before the end of the event. A central apnoea was scored if respiratory effort was absent throughout the duration of the event, the event lasted for at least two missed breaths and was associated with an arousal/awakening or a $\geqslant$3% desaturation. A hypopnoea was scored if the event was associated with a $\geqslant$50% fall in amplitude of the nasal pressure transducer, lasted at least for two breaths and was associated with an arousal/awakening or $\geqslant$3% desaturation. The obstructive apnoea–hypopnoea index (AHI) was calculated as the number of apnoeas and hypopnoea per hour of TST. Arousals were classified as either spontaneous or respiratory, and corresponding indices, namely the total arousal index (TAI) and the respiratory arousal index (RAI), were computed.

The diagnosis of OSA was defined by the presence of an AHI $\geqslant$ 2/h of total sleep time (hTST). Control children were non-snoring children with an AHI < 2/hTST.

2.2. Plasma assays

hsCRP was measured within 2–3 h after collection using the Flex reagent Cartridge (Date Behring, Newark, DE, USA), which is based on a particle-enhanced turbidimetric immunoassay technique. Serum levels of lipids, including total cholesterol, high-density lipoprotein (HDL) cholesterol, calculated low-density lipoprotein (LDL) cholesterol and triglycerides, were also assessed with a Flex reagent cartridge (Date Behring, Newark, DE, USA). Plasma insulin levels were measured using a commercially available radioimmunoassay kit (Coat-A-Count Insulin, Cambridge Diagnostic Products, Inc., Fort Lauderdale, FL, USA). Plasma glucose levels were measured using a commercial kit based on the hexokinase-glucose-6-phosphate dehydrogenase method (Flex Reagent Cartridges, Dade Behring, Newark, DE, USA). Insulin resistance was then assessed using the HOMA-IR equation (fasting insulin $\times$ fasting glucose/405) [20]. In addition, plasma samples were frozen at -80 °C till assay.

2.3. 25(OH)D assay

25(OH)D plasma levels were assessed using a commercially available kit (Eagle Biosciences; cat # VID31-K01). The assay exhibited a low-level detection threshold of 1.6 ng/ml, linearity up to 225 ng/ml and inter-assay and intra-assay coefficients of variability of 4.9% and 7.1%, respectively.

2.4. Statistical analysis

All analyses were conducted using Statistical Package for the Social Sciences (SPSS) software (version 19.0; SPPS Inc., Chicago, Ill, USA), and data are presented as mean ± standard deviation (SD). Since both OSA and obesity (OB) are associated with systemic low-grade inflammation, children were subdivided into four groups, based on the presence or absence of (OB) and OSA (i.e., non-obese with OSA (OSA-NOB), non-obese without OSA (NOSA-NOB), obese with OSA (OSA-OB) and obese without OSA (NOSA-OB)). Significant differences within groups were analysed using analysis of variance (ANOVA), followed by *post hoc* tests with Bonferroni corrections for multiple comparisons for continuous variables and chi-square tests for categorical variables. If the data were not normally distributed, they were logarithmically transformed. Spearman's correlation analyses were conducted to examine potential associations between BMI *z*-score, sleep variables, lipid profiles, hsCRP and HOMA and plasma concentrations of 25(OH)D, followed by stepwise logistic regressions. All *p*-values reported are two-tailed with statistical significance set at <0.05.

3. Results

A total of 176 children fulfilling entry criteria completed the overnight polysomnographic evaluation and provided a fasting blood sample after the sleep study. A total of 18 children refused to participate in the study (three parents declined to participate altogether and 15 parents were not willing to participate in the blood draw portion of the study). The demographic and polysomnographic characteristics of these 18 children were similar to those of the cohort, which are shown in Tables 1 and 2.

In general, AA children had lower 25(OH)D levels when compared to Caucasian children (69.9 ± 21.9 vs. 93.4 ± 22.5 ng/ml; $p < 0.0001$), and obese children had lower levels than non-obese children (83.6 ± 19.2 vs. 97.1 ± 20.9 ng/ml; $p < 0.01$). However, there were no differences in 25(OH)D according to age or according to gender. Similarly, we did not find any significant differences in mean values for the whole cohort between samples collected during winter season compared to summer season.

There were no significant differences in age, gender or ethnicity across the four subgroups. However, obese children exhibited higher BMI *z*-scores, as well as higher HOMA-IR, serum lipids and hsCRP levels and reduced HDL cholesterol levels. Similarly, children with OSA had significantly higher HOMA-IR, LDL cholesterol and hsCRP concentrations, and lower HDL cholesterol levels (Table 1).

Primary sleep disturbance measures clinically used to characterise the severity of OSA were not significantly different in obese and non-obese children with OSA. Similarly, there were no differences in sleep measures in obese and non-obese children without OSA (Table 2).

Obese children without OSA had lower 25(OH)D levels than non-obese children without OSA ($p < 0.01$; Table 1). Similarly, non-obese children with OSA also exhibited lower 25(OH)D levels compared to non-obese controls ($p < 0.01$; Table 1). However, obese children with OSA demonstrated the lowest 25(OH)D levels ($p < 0.01$; Table 1).

In order to estimate potential associations between 25(OH)D plasma levels, polysomnographic measures and metabolic indices, we initially performed bivariate Spearman correlation analyses (Fig. 1).Significant linear correlations emerged between 25(OH)D and AHI (Fig. 1A, $r = -0.285$, $p < 0.001$), nadir SpO_2 ($r = 0.283$, $p < 0.001$), BMI *z*-score (Fig. 1B; $r = -0.302$, $p < 0.0001$), HOMA-IR (Fig. 1C, $r = -0.259$, $p < 0.001$) and hsCRP (Fig. 1D, $r = -0.318$, $p < 0.001$), but not with RAI, total cholesterol, LDL or HDL cholesterol or triglyceride levels. Furthermore, we compared

Table 1
Characteristics of 176 obese and non-obese children with and without OSA.

	Non-obese with OSA (n = 57)	Non-obese without OSA (n = 38)	Obese with OSA (n = 45)	Obese without OSA (n = 36)
Age (years)	6.5 ± 0.9	7.1 ± 1.4	6.8 ± 0.9	7.2 ± 1.5
Gender (male, %)	56.1	52.6	55.5	52.7
Ethnicity (caucasian, %)	52.2	50.0	51.1	50.0
BMI z-score	0.22 ± 1.04[§]	0.16 ± 0.94[§]	2.42 ± 0.40[§]	2.38 ± 0.47[§]
Total cholesterol (mg/dl)	150.2 ± 21.8[**,§]	139.6 ± 19.2[**,§]	171.6 ± 40.0[**,§]	161.2 ± 32.1[**,§]
HDL cholesterol (mg/dl)	51.7 ± 15.2[**,§]	67.5 ± 12.29[§]	49.6 ± 11.9[**,§]	51.9 ± 12.8[**,§]
LDL cholesterol (mg/dl)	92.4 ± 21.3[**,§]	78.3 ± 18.9[**,§]	130.1 ± 28.9[**,§]	96.5 ± 21.3[**,§]
Tryglycerides (mg/dl)	60.7 ± 40.5[§]	53.2 ± 28.8[§]	79.7 ± 3481[§]	71.5 ± 33.8[§]
HOMA-IR	1.76 ± 0.92[**,§]	1.02 ± 1.15[**,§]	4.64 ± 1.83[**,§]	3.49 ± 2.95[**,§]
hsCRP (mg/dl)	5.08 ± 4.25	1.33 ± 2.29[**,§]	6.86 ± 4.40[**,§]	2.61 ± 2.45[**,§]
25(OH)D (ng/ml)	83.4 ± 24.9 [**,§]	94.8 ± 24.3[**,§]	67.7 ± 22.4[**,§]	81.1 ± 22.2[**,§]

HDL: high-density lipid cholesterol; LDL: low-density lipid cholesterol; hsCRP: high-sensitivity C-reactive protein.
[§] non-obese vs. obese – $p < 0.01$.
[**] OSA vs. no-OSA.

Table 2
Polysomnographic data of 176 obese and non-obese children with and without OSA.

	Non-obese with OSA (n = 57)	Non-obese without OSA (n = 38)	Obese with OSA (n = 45)	Obese without OSA (n = 36)
Total sleep duration (min)	478.7 ± 59.3	471.9 ± 48.5	471.1 ± 56.7	470.1 ± 54.9
Stage 1 (%)	7.5 ± 3.9[**]	5.0 ± 4.2[**]	8.8 ± 5.7[**]	5.6 ± 5.1[**]
Stage 2 (%)	38.9 ± 9.7	35.2 ± 8.5	43.9 ± 11.7	37.2 ± 9.9
Stage 3 (%)	36.6 ± 15.1[**]	45.4 ± 13.4[**]	37.2 ± 16.2	44.4 ± 13.4
REM sleep (%)	18.9 ± 6.9[**]	26.1 ± 8.7[**]	17.1 ± 9.2[**]	21.9 ± 10.5[**]
Sleep latency (min)	24.1 ± 18.3[**,§]	31.6 ± 17.1[**,§]	11.3 ± 10.9[**,§]	25.8 ± 17.4[**,§]
REM latency (min)	118.2 ± 61.1[**,§]	137.3 ± 55.1[**,§]	110.4 ± 58.2[**,§]	141.3 ± 58.7[**,§]
Total arousal index (events/hTST)	23.3 ± 11.8[**]	10.6 ± 7.2[**]	23.8 ± 12.6[**]	12.6 ± 7.5[**]
Respiratory arousal index (events/hTST)	7.2 ± 3.6[**,§]	0.1 ± 0.1[**,§]	8.8 ± 4.5[**,§]	0.7 ± 0.5[**,§]
Obstructive apnoea–hypopnoea index (events/hTST)	8.8 ± 8.4[**]	0.6 ± 0.5[**]	12.4 ± 13.4[**]	0.6 ± 0.6[**]
SpO_2 nadir (%)	84.6 ± 6.3[**]	95.9 ± 0.4[**]	83.7 ± 8.4[**]	92.1 ± 2.5[**]

All data are expressed as mean ± SD.
[§] non-obese vs. obese – $p < 0.02$.
[**] OSA vs. no-OSA – $p < 0.02$.

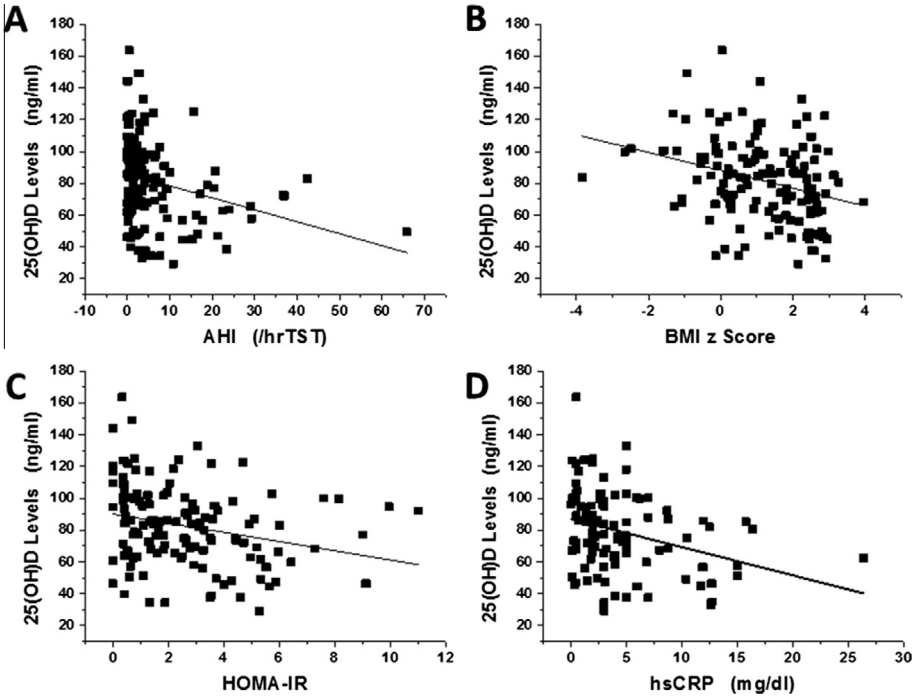

Fig. 1. Scatter plots of 25(OH)D plasma levels versus BMI z-score, obstructive apnoea–hypopnoea index (AHI), nadir SpO_2, hsCRP and HOMA-IR expression in a cohort of 176 children with and without obesity or OSA. Panel A $r = -0.285$, $p < 0.001$. Panel B $r = -0.302$, $p < 0.0001$. Panel C $r = -0.259$, $p < 0.001$. Panel D $r = -0.318$, $p < 0.001$.

Table 3
Multivariate regression analyses between anthropometric, demographic and polysomnographic measures, HOMA-IR, hsCRP, lipid profile and 25(OH)D levels.

Variables	25(OH)D plasma levels	
	Standardised coefficients	*p*-value
Age	0.008	0.976
Gender	0.004	0.981
Race	0.432	<0.0001
BMI-*z* score*	−0.167	<0.003
HOMA-IR**	−0.136	<0.01
LDL cholesterol	0.013	0.923
HDL cholesterol	0.079	0.897
hsCRP†	0.017	0.945
AHI†,***	−0.178	<0.01
SpO_2 nadir***	0.177	<0.01
Respiratory arousal index†	0.007	0.968

HDL: high-density lipid cholesterol; LDL: low-density lipid cholesterol; hsCRP: high-sensitivity C-reactive protein; AHI – obstructive apnoea–hypopnoea index; HOMA-IR – homeostatic model of insulin resistance.
† Data were log-transformed; data for age, gender and race are not adjusted.
* Data for BMI *z*-score are shown after adjusting for age, race and gender only.
** All other data are shown after controlling for age, gender, race and BMI *z* score.
*** All other data are shown after controlling for age, gender, race and BMI *z* score.

whether those children with clinically defined low 25(OH)D levels (<60 ng/ml; $n = 31$) differed from those with normal 25(OH)D levels and found that children with low 25(OH)D levels were of similar age and gender, but more likely to be AA (relative risk (RR): 1.76; 95% confidence interval (CI): 1.32–2.45; $p < 0.03$), to have increased BMI (BMI *z*-score: 1.8 ± 0.9 vs. 1.1 ± 1.3; RR for BMI *z*-score > 1.65: 1.67; 95% CI: 1.45–3.14; $p < 0.0001$), had more severe OSA (AHI: 11.3 ± 13.7/hTST vs. 4.75 ± 7.9/hTST; $p < 0.0001$), had higher hsCRP levels (6.7 ± 5.1 vs. 4.3 ± 3.7 mg/dl; $p < 0.001$) and higher total cholesterol (166.4 ± 40.7 vs. 152.7 ± 27.8; $p < 0.01$) and LDL cholesterol (105.6 ± 35.7 vs. 94.1 ± 24.4 mg/dl; $p < 0.01$) and HOMA-IR (3.8 ± 2.2 vs. 2.4 ± 2.2; $p < 0.001$) as well as lower HDL levels (.49.9 ± 13.5 vs. 57.8 ± 15.1 mg/dl; $p < 0.01$).

Therefore, to further explore whether AHI was an independent predictor of 25(OH)D levels, we performed stepwise multiple regression analyses with age, gender, ethnicity, BMI *z*-score, HOMA-IR and hsCRP included as potential confounders in the model. In the stepwise multiple regression model, AHI or SpO_2 nadir were independently associated with 25(OH)D levels, and accounted for 17.7% of the variance in 25(OH)D after controlling for race, BMI *z*-score, HOMA-IR and hsCRP (Table 3; $p < 0.01$).

4. Discussion

This study shows that both obese children and children with OSA exhibit significantly lower 25(OH)D plasma levels when compared to healthy controls, even when adjusted for ethnicity. Indeed, AA children consistently demonstrate markedly lower 25(OH)D plasma concentrations, a finding that has been corroborated in several previous studies and linked to insulin resistance and obesity [11,21–24]. Furthermore, we found that if both obesity and OSA are concurrently present, 25(OH)D levels are further reduced. Linear associations emerged between 25(OH)D plasma levels and BMI *z*-score as well as with the two of the major polysomnographic measures traditionally used to characterise OSA, namely AHI and SpO_2 nadir. Similarly, both HOMA-IR and hsCRP, as surrogate reporters of reduced insulin sensitivity and of low-grade inflammation, respectively, were significantly associated with circulating 25(OH)D levels, but this was not the case for any of the serum lipid measurements, even if such levels were different among children with clinically defined low 25(OH)D levels. These findings suggest that assessment of 25(OH)D plasma levels may provide a potential biochemical indicator for children with OSA at risk of end-organ morbidities [3,25,2].

Before we explore the potential implications of our findings, several methodological issues deserve mention. First, the prospective recruitment approach enabled careful standardisation of blood collection procedures, which coincided with a very narrow time window, that is, immediately after the overnight sleep study. Therefore, not only were fasting conditions strictly enforced, but any circadian variance in any of the plasma measures was also avoided by the uniformity of sampling times. In addition, the duration of sleep during the night preceding the blood draw was available as derived from the polysomnogram, and did not significantly differ among the four subgroups. It remains thus far unknown whether sleep restriction, either acute or chronic, will alter 25(OH)D levels. Based on current findings, sleep fragmentation, as indicated by the RAI, was not significantly associated with 25(OH)D concentrations. First, it is unlikely that perturbations of sleep will lead to altered vitamin D bioavailability. Second, all of the 25(OH)D assays were conducted using same batch commercial assays and were performed concomitantly, thereby reducing additional sources of assay variability. Third, we should indicate that the sample collection was evenly distributed along the calendar year without seasonal preference, such that the effect of season did not emerge among our findings. Finally, we did not thoroughly investigate for the presence of asthma in our cohort. In this context, vitamin D deficiency appears to be associated with a greater risk of asthma [26,27], even if the 25(OH)D levels do not correlate with the severity of asthma [28]. Of note, we and others have previously reported on the potential association between asthma and OSA in children [29,30].

We are unaware of published studies in children with OSA examining whether alterations are present in 25(OH)D levels. As mentioned above, two small studies assessing vitamin D levels in children undergoing surgical adenotonsillectomy that did not incorporate polysomnographic recordings yielded conflictive results [16,17]. In a large cohort of >800 adult patients with OSA, an inverse association of 25(OH)D with diabetes and metabolic syndrome was reported by Barceló and collaborators [31]. Similarly, another study involving 190 adult patients with OSA showed that those patients with more severe OSA polysomnographic indices were more likely to exhibit reduced vitamin D levels that were in turn linearly correlated to the presence of insulin resistance [32]. Thus, the inverse linear relationships identified herein between vitamin D levels and metabolic and inflammatory markers as well as with AHI and nadir SpO_2 would potentially suggest the possibility that administration of supplemental vitamin D could ameliorate aspects of the paediatric OSA clinical phenotypic spectrum [1,33]. If current findings are confirmed in future studies, implementation of a randomised clinical trial involving pharmacological administration of exogenous vitamin D might be warranted [34].

In the context of the recently uncovered functional roles of 25(OH)D [35], it was expected that the decline in 25(OH)D levels in both obese and OSA children would be associated not only with correlates of insulin resistance (i.e., HOMA-IR), but also with previously described alterations in serum lipid profiles and hsCRP, the latter serving as a reporter for low-grade systemic inflammation [6–14,36]. Indeed, both HOMA-IR and hsCRP were strongly and independently associated with 25(OH)D levels, suggesting the intriguing possibility that reduced biological availability and activity of 25(OH)D in clinical settings, such as obesity or OSA, may facilitate the emergence of insulin resistance and other OSA-induced morbidities. The potentiation of the effect of obesity and OSA when jointly present on 25(OH)D plasma concentrations was also confirmed in the present study. Although it remains unclear whether obesity and OSA exert their effects via similar and overlapping pathways or not, it is possible that these chronic systemic inflammatory states may ultimately result in reduced bioavailability of 25(OH)D, the latter then potentiating some of

the adverse effects of the two underlying disorders. Conversely, it cannot be excluded that specific extraneous factors leading to lower 25(OH)D concentrations may promote pro-inflammatory states that exaggerate the proliferation of upper airway lymphadenoid tissues, thereby favouring more severe OSA among susceptible individuals. Furthermore, obese children with OSA are more likely to consume a skewed and unbalanced diet primarily composed by energy-dense food items [37,38] that may lead to reduced intake of essential vitamins, such as vitamin D.

In summary, we have shown that the presence of obesity and the presence of sleep-disordered breathing in children are associated with reduced plasma levels of 25(OH)D and that 25(OH)D levels are strongly associated with measures of insulin resistance and hsCRP, but not with dyslipidemia. Improved understanding of the causal pathways underlying these associations may not only offer clinical diagnostic opportunities, but also enable delineation of therapeutic interventions targeting vitamin D and aiming for example to reduce the magnitude and risk for development of some of the morbid consequences of paediatric OSA.

Funding

DG is supported by National Institutes of Health grants HL-65270, HL-086662 and HL-107160.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2013.12.009.

Acknowledgements

LKG provided conceptual initiative and design for the project, recruited subjects, analysed sleep data and metabolic data, drafted components of the manuscript and analysed data. EP performed experiments and analysed data. DG provided the conceptual design of the project, analysed data, drafted the manuscript and is responsible for the financial support of the project and the manuscript content. Drs. Leila Kheirandish-Gozal and David Gozal are the guarantors of this work, had full access to all the data and take full responsibility for the integrity of data and the accuracy of data analysis. All authors have reviewed and approved the final version of the manuscript.

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